UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/041,821	10/19/2001	Christopher T. Culbertson	1875-P02617US0	4567

110 7590 06/18/2003

DANN, DORFMAN, HERRELL & SKILLMAN
1601 MARKET STREET
SUITE 2400
PHILADELPHIA, PA 19103-2307

EXAMINER
NOGUEROLA, ALEXANDER STEPHAN

ART UNIT	PAPER NUMBER
1753	6

DATE MAILED: 06/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/041,821	CULBERTSON ET AL.	
	Examin r	Art Unit	
	ALEX NOGUEROLA	1753	

-- Th MAILING DATE of this communication appears on the cover sh et with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-42 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) 39 is/are allowed.

6)☒ Claim(s) 1-7,9,11,19-21,24-33 and 40-42 is/are rejected.

7)☒ Claim(s) 8,10,12-18,22,23 and 34-38 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 19 October 2001 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Claim Objections

1. Claim 39 objected to because of the following informality: in line 12 "channel" should be -- microchannel --. Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. Claims 40-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention:

a) Claim 40 depends from itself; and

b) Claim 40 requires that the particle be a cell. Claims 41 and 42 which depend from claim 40 allows the particle to be something other than a cell

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 1, 2, 4-7, 9, 19, 24-26, and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Burdon et al. (US 6,572,830 B1).

Addressing claim 1, Bourdon et al. teach a method of releasing the intracellular contents of at least one cell of a cell-containing fluid sample for analysis, the method comprising the steps of

a) providing a substrate having a microchannel structure which includes at least one microchannel therein (the abstract; Figure 12; and col. 16, ll. 5-16);

b) generating an electric field from a source of electric potential, the electric field being applied in a spatially defined region of the at least one microchannel, comprising a cell lysis region and having sufficient strength to induce cell lysis (implied by col. 16, ll. 45-59 and col. 17, ll. 11-42, which teaches how to apply an electric field to a cavity within the device to lyse cells); and

c) positioning the at least one cell of the fluid sample in the cell lysis region for a time sufficient to release the intracellular contents of the at least one cell into the fluid sample, thereby providing a volume of analyte in the at least one microchannel (implied by col. 16, ll. 45-59 which teaches that cell lysing is an important process for which the device can be used).

Addressing claim 2, as seen in col. 16, ll. 12-14, sample flows into the lysis cavity through channels 448 or 450.

Addressing claims 4 and 5, electroosmotic pumping and electrohydrodynamic pumping are taught in col. 24, ll. 10-20.

Addressing claim 6, chemical lysing is disclosed in col. 16, ll. 52-56 and col. 16, ll. 60-67.

Addressing claim 7, a substantially constant electric lysing field is disclosed in col. 17, ll. 11-17, which discloses a range of DC voltage gradients that can be used.

Addressing claim 9, an electric lysing field that varies over time is taught in col. 17, ll. 25-42.

Addressing claim 19, Burdon et al. teach detecting light at various locations within the microchannel structure and monitoring changes in the incident light (col. 22, ln. 12 – col. 23, ln. 53)

Addressing claim 24, as seen in col. 17, ll. 25-42 the electric field is oriented perpendicularly to the direction of flow of the cell-containing fluid sample.

Addressing claim 25, Burdon et al. teach a microfluidic system for transport and lysis of at least one cell of a cell-containing fluid sample, the system comprising a source of electric potential (col. 17, ll. 12-14 and col. 17, ll. 35-39) and a solid substrate having at least one microchannel with a longitudinal axis (element 554 in Figure 16), the microchannel having a first wall portion on one side of the axis, a second wall portion on another side of the axis and a cell lysis region between the first and second wall portions, a first and second electrical contact positioned adjacent the first and second wall portions of the at least one microchannel (elements 556 and 558 in Figure 16), the first and second electrical contacts being spatially separated by the cell lysis region and being electrically isolated from one another (Figure 16), the first and second electrical contacts being connected to the source of electrical potential which is operative to apply an electric field to the cell lysis region within the microchannel space between the first and second electrical contacts (elements 560 and 562 in Figure 16 and col. 17, ll. 11-42), and means for transporting the cell-containing fluid sample along the at least one microchannel (col. 24, ll. 10-53).

Addressing claim 26, that the first and second walls are on opposite sides other longitudinal axis may be seen from Figure 16.

Addressing claim 29, that the electrical contacts extend and are coextensive as claimed is implied by Figure16.

5. Claims 1, 2, 7, and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Tai et al. (WO 99/25816 A1).

Addressing claim 1, Tai et al. teach a method of releasing the intracellular contents of at least one cell of a cell-containing fluid sample for analysis (the abstract), the method comprising the steps of

a) providing a substrate having a microchannel structure which includes at least one microchannel therein (Figure 2D and pg. 4, ll. 12-15);

b) generating an electric field from a source of electric potential, the electric field being applied in a spatially defined region of the at least one microchannel, comprising a cell lysis region and having sufficient strength to induce cell lysis (pg. 4, ll. 21-29); and

c) positioning the at least one cell of the fluid sample in the cell lysis region for a time sufficient to release the intracellular contents of the at least one cell into the fluid sample, thereby providing a volume of analyte in the at least one microchannel (pg. 4, ll. 21-29 and pg. 5, ll. 25 – pg. 6, ln. 5).

Addressing claim 2, as seen in Figure 2D sample flows into the lysis cavity through inlet channel 220.

Addressing claim 7, lysing with a substantially constant electric field is taught in page 5, ln. 25 – pg. 6, ln. 13.

Addressing claim 24, as seen in Figure 2D the electric field is oriented perpendicularly to the direction of flow of the cell-containing fluid sample.

6. Claims 1, 2, 4-7, 9, 11, 19, 20, 25, 26, and 29-33 are rejected under 35 U.S.C. 102(e) as being anticipated by Briscoe et al. (US 6,544,734 B1).

Addressing claim 1, Briscoe et al. teach a method of releasing the intracellular contents of at least one cell of a cell-containing fluid sample for analysis, the method comprising the steps of

a) providing a substrate having a microchannel structure which includes at least one microchannel therein (the abstract; Figures 3-4A; and col. 8, ll. 10-51, especially lines 33-47);

b) generating an electric field from a source of electric potential, the electric field being applied in a spatially defined region of the at least one microchannel, comprising a cell lysis region and having sufficient strength to induce cell lysis (col. 3, ll. 39-53); and

c) positioning the at least one cell of the fluid sample in the cell lysis region for a time sufficient to release the intracellular contents of the at least one cell into the fluid sample, thereby providing a volume of analyte in the at least one microchannel (col. 3, ll. 39-53).

Addressing claim 2, as seen in col. 3, ll.40-46 sample flows into the lysis cavity through inlet port 12.

Addressing claims 4 and 5, electroosmotic pumping is taught in col. 3, ll. 24-33.

Addressing claim 6, chemical lysising is disclosed in col. 3, ll. 52-53.

Addressing claim 7, a substantially constant electric lysing field is disclosed in col. 3, ll. 49-51, which discloses a range of DC voltage gradients that can be used.

Addressing claims 9 and 11, a pulsed electric lysing field is taught in col. 11, ll. 7-12.

Addressing claim 19, analyzing analyte beyond the cell lysis region is taught in col. 3, ll. 40-53 together with col. 5, ll. 3-20.

Addressing claim 20, electrophoresis is taught in col. 5, ll. 3-10.

Addressing claim 25, Briscoe et al. teach a microfluidic system for transport and lysis of at least one cell of a cell-containing fluid sample (the abstract), the system comprising a source of electric potential (implied by col. 3, ll. 49-51) and a solid substrate having at least one microchannel with a longitudinal axis (the region between electrodes 356 and 358 in Figure 4), the microchannel having a first wall portion on one side of the axis, a second wall portion on another side of the axis and a cell lysis region between the first and second wall portions (the region between electrodes 356 and 358 in Figure 4), a first and second electrical contact positioned adjacent the first and second wall portions of the at least one microchannel (electrodes 356 and 358 in Figure 4), the first and second electrical contacts being spatially separated by the cell lysis region and being electrically isolated from one another (Figure 4), the first and second electrical contacts being connected to the source of electrical potential which is operative to

apply an electric field to the cell lysis region within the microchannel space between the first and second electrical contacts (implied by col. 3, ll. 49-51), and means for transporting the cell-containing fluid sample along the at least one microchannel (col. 3, ll. 24-33).

Addressing claim 26, that the first and second walls are on opposite sides other longitudinal axis may be seen from Figure 3.

Addressing claim 29, that the electrical contacts extend and are coextensive as claimed may be seen in Figure 3.

Addressing claim 30, Briscoe et al. teach a microfluidic system for transport and lysis of at least one cell of a cell-containing fluid sample and separation of the intracellular contents of the at least one cell, the system comprising a solid substrate having at least one microchannel disposed therein (the region between electrodes 188 and 190 in Figure 3), the microchannel having a cell transport segment and a separation segment having a first and second end portions (element 156 is an inlet port (transport segment) and element 170 is a separation chamber (separation segment)), intermediate the transport segment and separation segment, and spatially separated from one another, the microchannel space between the electrical contacts defining a cell lysis region (150), the electrical contacts being connected to a source of electric potential to apply an electric field to the cell lysis region (implied by col. 3, ll. 49-51); means for flowing the cell-containing fluid sample through at least one microchannel (col. 11, ll. 12-25); and means

between the first and second separation segment end portions for effecting separation of the intracellular contents of the at least one cell (col. 13, ll. 17-32).

Addressing claim 31, as seen in Figure 3, the cross-sectional area of the transport segment of the microchannel is different than the cross-sectional area of the lysis region.

Addressing claim 32, as seen in Figure 3, the cross-sectional area of the lysis region is constricted relative to the DNA amplification region (154).

Addressing claim 33, as seen in Figure 3, the cross-sectional area of the lysis region is expanded relative to the transport region (156).

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-3, 11, 19-21, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al. (WO 99/38612 A1).

Addressing claim 1, Cheng et al. teach a method of releasing the intracellular contents of at least one cell of a cell-containing fluid sample for analysis (the abstract), the method comprising the steps of

a) providing a substrate having a microchannel structure which includes at least one channel therein (the abstract; Figure 11A; and pg. 9, ll. 10-15);

b) generating an electric field from a source of electric potential, the electric field being applied in a spatially defined region of the at least one microchannel, comprising a cell lysis region and having sufficient strength to induce cell lysis (pg. 15, ll. 3-10); and

c) positioning the at least one cell of the fluid sample in the cell lysis region for a time sufficient to release the intracellular contents of the at least one cell into the fluid sample, thereby providing a volume of analyte in the at least one microchannel (pg. 15, ll. 3-15).

Cheng et al. do not mention whether the channels (18a-18c in Figure 12) are microchannels. However, it would have been obvious to one with ordinary skill in the art at the time the invention was made to use microchannels because the flow chamber only has a volume of 10 μl (pg. 9, ln. 13).

Addressing claim 2, as seen in pg. 21, ll.6-7 sample flows into the lysis cavity through inlet tubing 18a.

Addressing claim 3, using a peristaltic pump to cause flow into the lysis cavity is taught in pg. 14, ll. 8-9.

Addressing claim 11, a pulsed electric lysing field is taught in page 15, ll. 3-10.

Addressing claim 19, analyzing analyte beyond the cell lysis region is implied by page 21, lines 4-14, which teaches moving the lysate beyond the lysing region subjecting the lysate to hybridization or "some other enzymatic reaction".

Addressing claim 20, performing electrophoresis on the lysate is also taught in page 15, lines 15-29.

Addressing claim 21, performing DNA hybridization assay with an oligonucleotide capture probe specific for a certain region of DNA plasmid is taught in page 15, line 30 – page 16, line 5.

Addressing claim 24, as seen in Figure 11A the electric field is oriented perpendicularly to the direction of flow of the cell-containing fluid sample.

9. Claims 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Briscoe et al. (US 6,544,734 B1) in view of Wolk et al. (US 6,322,683 B1).

Briscoe et al. teach a microfluidic system for transport and lysis of at least one cell of a cell-containing fluid sample (the abstract), the system comprising a source of electric potential (implied by col. 3, ll. 49-51) and a solid substrate having at least one microchannel with a longitudinal axis (the region between electrodes 356 and 358 in Figure 4), the microchannel having a first wall portion on one side of the axis, a second wall portion on another side of the axis and a cell lysis region between the first and second wall portions (the region between electrodes 356 and 358 in Figure 4), a first and second electrical contact positioned adjacent the first and second wall portions of the at least one microchannel (electrodes 356 and 358 in Figure 4), the first and second electrical contacts being spatially separated by the cell lysis region and being electrically isolated from one another (Figure 4), the first and second electrical contacts being connected to the source of electrical potential which is operative to apply an electric field to the cell lysis region within the microchannel space between the first and second electrical contacts (implied by col. 3, ll. 49-51), and means for transporting the cell-containing fluid sample along the at least one microchannel (col. 3, ll. 24-33).

Additionally, using a pump (hydraulic force application means) is disclosed in col. 3, ll. 17-29 and implied by col. 11, ll. 12-17, which discloses using pressure, but the location of the pump is not disclosed. As shown by Wolk et al., for example, a positive pressure pump (which would be located downstream relative to the fluid flow path) or a negative pressure pump (which would be located upstream relative to the fluid flow path) were commonly used at the time of the invention to move fluid through microfluidic devices (col. 4, ll. 20-34). Barring evidence to the

contrary, such as unexpected results, the choice of positive pressure pump or negative pressure pump is just a matter of optimization or convenience. For, example, it may be more convenient to place a positive pressure pump near the entrance to the microfluidic system so that it could more easily accessed for cleaning or maintenance.

Allowable Subject Matter

10. Claim 39 is allowed.

11. Claims 8, 10, 12-18, 22, 23, and 34-38 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

12. Claims 40-42 would be allowable if rewritten to overcome the rejections under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

13. The following is a statement of reasons for the indication of allowable subject matter:

a) Claims 8 and 10: neither Burdon et al. nor Tai et al. mention activating electric lysing field in response to a detected change in conductivity caused by passage of at least one cell through the microchannel. Tai et al. applied an attraction waveform for a short time to draw

cells into the lysis chamber and then started the lysing phase (pg. 5, ll. 29-33). Burdon et al. monitor sample presence or absence in channels and wells by detecting a change in capacitance or conductivity in the channels or wells (col. 18, ln. 5 – col.19, ln. 11); however, there is no teaching of activating the electric lysing field in response to a change in conductivity;

b) Claim 12: Cheng et al. do not mention activating an electric lysing field in response to a detected change in conductivity caused by passage of at least one cell through the microchannel. Cheng et al. only state that after washing the cells retained in the lysis chamber lysis was performed (pg. 14, ln. 29 – pg. 15, ln. 6);

c) Claim 13 depends from allowable claim 12;

d) Claims 14-16: Burdon et al. teach detecting light at various locations within the microchannel structure, including the microchannel, and monitoring changes in the incident light (col. 22, ln. 12 – col. 23, ln. 53, especially col. 22, ll. 62-65), but they do no mention activating the electric lysing field in response to a change in response to scattered light. They use the light to monitor fluid flow and fluid composition. Cheng et al. and Briscoe et al. only teach using optical detection for locating analytes of interest (pg. 19, ll. 10-18 in Cheng et al. and col. 13, ll. 34-55 in Briscoe et al.);

e) Claim 17 depends from allowable claim 16;

f) Claim 18: none of the prior art of record disclose varying the strength of electric lsying field by varying at least one cross-sectional dimension of the microchannel within the cell lysis region;

g) Claim 22: Cheng et al. do not mention electrospraying the discrete segment for analysis by mass spectrometry. They perform DNA hybridization with optical detection;

h) Claim 23: Burdon et al., Tai et al., and Cheng et al. only disclose a lysing electric field oriented transverse with the direction of flow of the cell-containing fluid sample. Briscoe et al., is silent as to the orientation of the lysing electric field;

i) Claim 34: Briscoe et al. only teach using optical detection for locating analytes of interest (col. 13, ll. 34-55 in Briscoe et al.);

j) Claims 35-38 depend directly or indirectly from allowable claim 34; and

k) Claim 39 requires the step of introducing a chemical lysing solution through the second microchannel into the intersection of a first microchannel with a second microchannel, whereby the at least one compound is released into the fluid sample, thereby providing a volume of analyte in the intersection. In Tooke et al. chemical lysing solution is introduced from above or below the substrate as the second microchannels (5) are used for analyzing the lysate (page 12, line. 10 – page 13, line16). In the chemical lysing embodiment of Burdon et al. the chemicals necessary for lysing are introduced into the cavity 24 in Figure 1 via channel 26 (col. 16, ll. 60-67); and

l) Claims 40-42 appear to have been intended to depend directly or indirectly from allowable claim 39.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEX NOGUEROLA whose telephone number is (703) 305-5686. The examiner can normally be reached on M-F 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, NAM NGUYEN can be reached on (703) 308-3322. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9310 for regular communications and (703) 872-9311 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0661.

Alex Noguerola
June 13, 2003